Applicant :	Louis Casteilla Luc Penicaud Catherine Dacquet Pierre Renard
Serial N°:	US Serial No. 10/530,771
Filed :	April 7, 2005
Title :	Association between a ligand of peroxisome proliferators activated receptors and an antioxidant agent and pharmaceutical compositions containing them
Art Unit :	1614
Examiner :	Savitha Rao

Honorable Commissioner of Patents
PO Box 1450
Alexandria VA 22313

DECLARATION Under 37 CFR 1.132

I, Catherine DACQUET, a citizen of France, of 116, rue Charles Le Bon, 59650 Villeneuve d'Ascq, France, declare and say that :

I am research project leader at the Les Laboratoires Servier, Paris. My interest of investigation consists of drug discovery research. I refer to my CV for an extensive overview of my backgrounds and qualifications, of which a copy is attached as Annex I.

I am the co-inventor of US Patent Application Serial n° 10/530,771 filed April 7, 2005 concerning "Association between a ligand of peroxisome proliferators activated receptors and an antioxidant agent and pharmaceutical compositions containing them".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological and chemical data contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the therapeutic interest and utility of the associations described.

One additional example with regard to US Patent application n° 10/530,771 of association of rosiglitazone and coenzyme Q10 demonstrate the surprising effect of the associations according to the invention :

Protocol of the additional example :
Male C57 Black 6 ob/ob mice from 8 to 12 weeks old were used. After being placed in quarantine for one week, they were weighed and then randomised as a function of their weight and 6 homogeneous groups (starting weights not significantly different) were formed. After being weighed, the various compounds under test were injected by the intraperitoneal route once a day for 14 days. The compounds were injected in a solution of DMSO 5 % / Solutol 15 % / qsp H2O heated at 65°C to ensure good dissolution. In addition, the solution was pre-heated before injection. The mice were weighed every day and the weight obtained after 7 days of treatment was recorded.

Figure 1 :
Insulinemia of mice treated with the association rosiglitazone and coenzymeQ10 is reduced of 85% whereas the association of fenofibrate and coenzymeQ10 the insulinemia is only reduced of 42%. This difference is significant $p<0.01$.

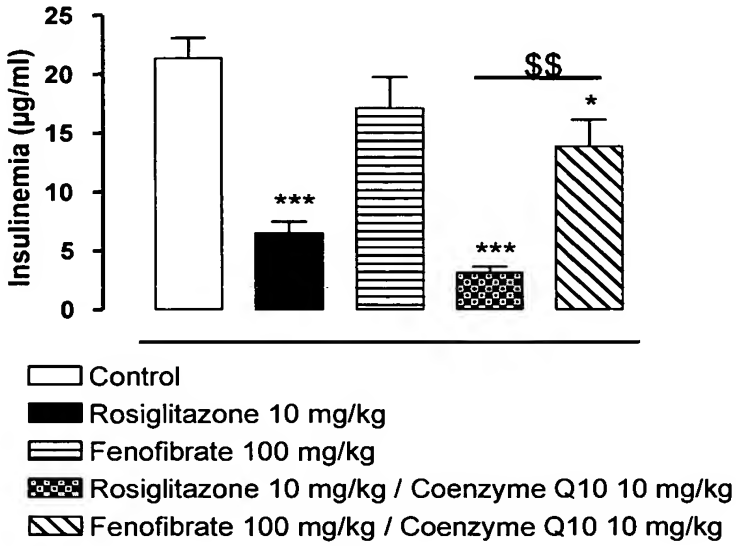
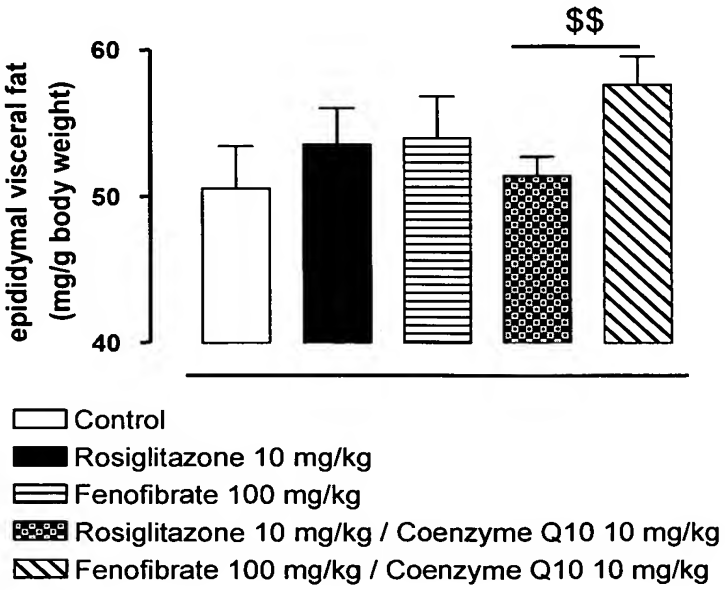


Figure 2 :
The results obtained with the association of rosiglitazone + coenzyme Q_{10} are indicated below and are expressed as the percentage epididymal visceral fat change with respect to the control (corresponding to mice treated with the injection solvent for 7 days). The weight of epididymal visceral fat has reduced in mice treated with rosiglitazone + coenzyme Q_{10} whereas then weight of epididymal visceral fat has increased in mice treated with fenofibrate + coenzyme Q_{10}.



Therefore, the results obtained from examples 1 and 2 clearly show :
- that the association enables the weight of epididymal visceral fat of obese mice to be reduced significantly,
- that there exists a synergy between the two components rosiglitazone and coenzymeQ10 of the association, the weight loss of epididymal visceral fat found being much greater in the case of the association of the invention than in the case of each component administered on its own and than the association fenofibrate plus coenzymeQ10.

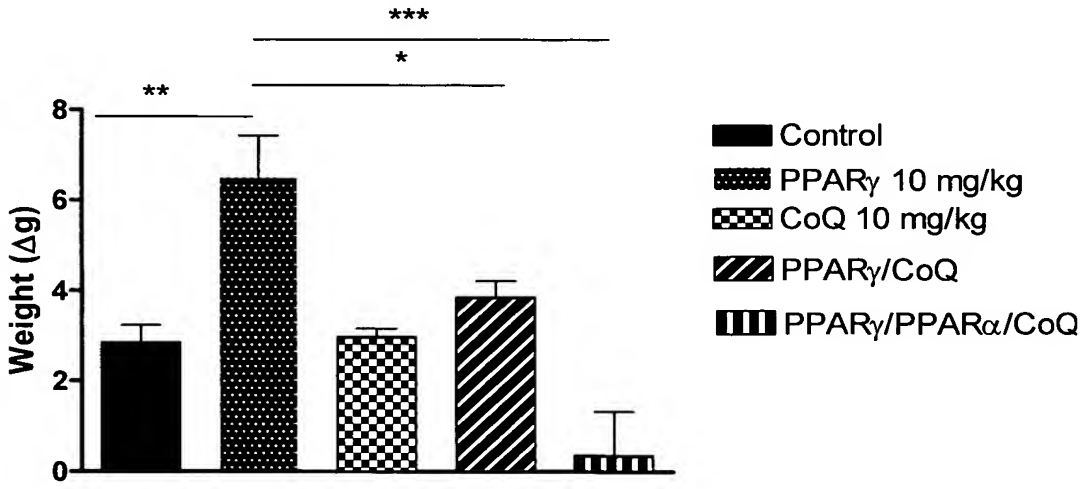
The following data correspond to quantitative data of example A in the description of the US patent n° 10/530,771. We observe that the weight of obese mice is reduced of 2.66g between mice treated with PPARγ (6.52g +/-0.91) and mice treated with PPARγ + coenzyme Q_{10} (3.86g +/-0.36). Thus in view of these quantitative data, the weight loss is less or equal to 2.5 grams in accordance with the previous argument.

Control : 2.86 +/- 0.38 (n=8)
PPARγ (Rosiglitazone)10 mg/kg 6.52 +/-0.91 (n= 7)
CoQ_{10} 10mg/kg 2.98 +/- 0.18 (n=8)
PPARγ (Rosiglitazone) 10 mg/kg / CoQ_{10}10 mg/kg: 3.86 +/ 0.36 (n=6)
PPARγ (Rosiglitazone) 10 mg/kg /PPARα10 mg/kg /CoQ_{10}10 mg/kg : 0.36 +/-0.97 (n=6)

The additive synergy is pharmacologic effect of two active principles equal to the sum of each effects : E(A + B) = E(A)+E(B) whereas potentiate synergy is pharmacologic effect of two active principles higher to the sum of each effects : E(A + B) > E(A)+E(B).

The quantitative data of Example A demonstrate a synergistic effect :
- the weight of obese mice is reduced of 2.66g between mice treated with PPARγ (6.52g +/-0.91) and mice treated with rosiglitazone (PPARγ) + coenzyme Q_{10} (3.86g +/-0.36);
- coenzyme Q_{10} alone is equal to the control and thus has no effect on the weight of obese mice.

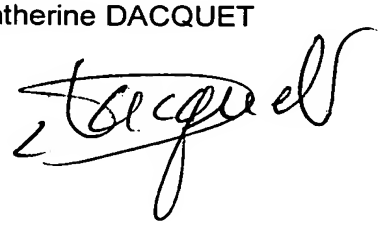
Thus in view of these quantitative data, the loss of weight is potentiate by coenzyme Q_{10} which individually has no effect on the weight of obese mice. The weight loss is at least equal to 2.5 grams, thus the pharmacologic effect of the association of rosiglitazone + coenzyme Q_{10} is higher to the effect of rosiglitazone (remind that coenzyme Q_{10} has no effect on the weight of obese mice). Therefore, these quantitative data prove the potentiate synergy of the association of rosiglitazone + coenzyme Q_{10}.



I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

Catherine DACQUET



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ANNEX 1

CURRICULUM VITAE

Catherine Dacquet joined the Institut de Recherches Servier, Division of Molecular and Cellular Pharmacology in 1993 as a team leader where she was in charge of the screening of new compounds. She carried out assays development, test standardization using binding technology and several cellular systems. She then moved to the External Therapeutic Division in 1999 as a research project leader where she was in charge of the coordination of PPAR Research Project mainly focused to built a scientific network in partnerships with internal and external collaborations. She continue this project on the Division of Metabolic Disease since 2004 managing the in vitro and in vivo pharmacology.
Prior to joining Servier, Catherine Dacquet was head of the laboratory of Pharmacology in Innothera, pharmaceutical industry specialized in the research of new molecules in the field of phlebologia. She had the responsibility of managing the drug discovery and the advanced projects to identify drugs for the treatment venous insufficiency.
She obtained her Pharm D from the University of Bordeaux in 1984 and her PhD in 1988 with a thesis on the mechanism of the calcium antagonists on vascular voltage-dependent calcium channels.

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